PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Bakka, Joan Jensen
PLOUGMANN & VINGTOFT A/S
Sundkrogsgade 9
P.O. Box 831
DK-2100 Copenhagen
DANEMARK

by fax and post

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	21.07.2004 30.07.04
Applicant's or agent's file reference: 32174PC01	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00263	22.04.2003	19.04.2002

Applicant: ASTION DEVELOPMENT A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Pfitzner, G Tel. +49 89 2399-8032

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 32174PC01	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00263	International filing date *(day/month/year)* 22.04.2003	Priority date *(day/month/year)* 19.04.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/726		
Applicant ASTION DEVELOPMENT A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.11.2003	21.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Uiber, P Telephone No. +49 89 2399-8474

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00263

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34 as originally filed

Claims, Numbers

1-41 filed with telefax on 14.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00263

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 26-41

because:

☒ the said international application, or the said claims Nos. 26-41 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-41
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-41
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-41
	No:	Claims	26-41

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/DK 03/00263

SECTION III

1). Claims 26-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

SECTION V

2). For the assessment of the present claims 26-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3). The following documents (D1-D5) are referred to in this written opinion; the numbering results from the order of citations found in the Search Report and it will be adhered to in the rest of the procedure. **It will be made reference to the cited passage(s) for each citation unless otherwise specified.**

4). In view of the restriction in scope of claim 1 , its subject-matter is novel over any of D1-D5 (Art. 33(2) PCT). D1 does not specify the derivatization of the aminosugar as presently claimed.

5). D1 which discloses the similar complex and compositions containing it, was concerned with the improved stability of the thus resulting composition. It is not concerned with the immunostimulation. The remaining documents D2-D5 already report the effectiveness of either the beta-2 adrenoreceptor agonist or said aminosugar in various inflammatory disorders, however taking separately. The problem posed in the present application can be seen as providing a new therapy in the treatment of immune-related disorders. The solution, according to the Applicant, was the use of said combination as stated in claim 1. Surprisingly, the Applicant has evidenced that such combinations achieve a synergistic activity (see Table on page 29). The skilled man could not have derived said effect from the prior art, accordingly, the subject matter of claim 1 involves an inventive step over the available cited prior art, D1-D5 (Ar. 33(3) PCT).

6). Items 4 and 5 also apply to claims 2-41.

CLAIMS

(AMENDED AFTER TELEPHONE INTERVIEW)

1. A chemical complex comprising:

i) a beta-2 adrenoceptor agonist; and
ii) an aminosugar selected from the group consisting of glucosamine, mannosamine, salts and derivatives thereof, wherein the derivatives thereof is selected from the group consisting of derivatives wherein the amino group and/or hydroxyl group of the aminosugar is alkylated, arylated or acylated, and wherein the anomeric, 2-, 3-, 4-, or 6-position is sulphated or phosphorylated.

2. A chemical complex according to claim 1, wherein the beta-2 adrenoceptor agonist is selected from the group consisting of bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, clorprenaline, dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, isoetarine, isoproterenol, mabuterol, metaproterenol, methoxyphenamine orciprenaline, pirbuterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salbutamol (albuterol), salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, derivatives and salts thereof.

3. The chemical complex according to any one of preceding claims, wherein the aminosugar is glucosamine hydrochloride or glucosamine sulfate.

4. The chemical complex according to any one of preceding claims, wherein the beta-2 adrenoceptor agonist is salbutamol sulfate, terbutaline sulfate or formoterol fumarate dihydrate.

5. A composition comprising:
i) a beta-2 adrenoceptor agonist;
ii) an aminosugar selected from the group consisting of glucosamine, mannosamine, salts and derivatives thereof, wherein the derivatives thereof is selected from the group consisting of wherein the amino group and/or hydroxyl group of the aminosugar is alkylated, arylated or acylated, and wherein the anomeric, 2-, 3-, 4-, or 6- position is sulphated or phosphorylated; and
iii) one or more acceptable excipients or carriers.

6. The composition according to claim 5, wherein the beta-2 adrenoceptor agonist is selected from the group consisting of bambuterol, bitolterol, carbuterol, clenbuterol, clorprenaline, dioxethedrine, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, formoterol, hexoprenaline, isoetarine, isoproterenol, mabuterol, metaproterenol, methoxyphenamine, pirbuterol, procaterol, protokylol, reproterol, rimiterol, ritodrine, salbutamol (albuterol), salmeterol, soterenol, terbutaline, tretoquinol, tulobuterol, derivatives and salts thereof.

AMENDED SHEET

7. The composition according to any one of claims 5 or 6, wherein the aminosugar is glucosamine hydrochloride or glucosamine sulfate.

8. The composition according to any one of claims 5 to 8, wherein the beta-2 adrenoceptor agonist is salbutamol sulfate, terbutaline sulfate or formoterol fumarate dihydrate.

9. The composition according to claim 5, wherein the beta-2 adrenoceptor agonist and the aminosugar is in the form of a chemical complex as defined in any one claims 1-4.

10. The composition according to any one of claims 5 to 10 further comprising one or more therapeutically active agents other than a beta-2 adrenoceptor agonist and the aminosugar.

11. The composition according to any one of claims 5 to 10 in a form selected from the group consisting of oral formulation, topical formulation, transdermal formulation, and parenteral formulation.

12. Use of a combination of a beta-2 adrenoceptor agonist and an aminosugar for the preparation of a medicament for the suppression of hypersensitivity and/or inflammatory reactions in a mammal, the aminosugar being selected from the group consisting of glucosamine, mannosamine, salts and derivatives thereof, wherein the derivatives thereof is selected from the group consisting of wherein the amino group and/or hydroxyl group of the aminosugar is alkylated, arylated or acylated, and wherein the anomeric, 2-, 3-, 4-, or 6- position is sulphated or phosphorylated.

13. The use according to claim 12, for the preparation of a medicament for treating a hypersensitivity skin disease

14. The use according to claim 13, wherein the hypersensitivity skin disease is selected from the group consisting of atopic eczema, contact dermatitis, seborrhoeic eczema and psoriasis.

15. The use according to claim 14, for the preparation of a medicament for the treatment of contact dermatitis or psoriasis.

16. The use according to claim 12, for the preparation of a medicament for the treatment of an autoimmune disease.

17. The use according to claim 16, wherein the autoimmune disease is selected from the group consisting of autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hemolytic anemias, Grave's disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyreoiditis, Autoimmune adrenalitis, Crohn's Disease, Ulcerative Colitis, Glomerulonephritis,

Progressive Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Rheumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue Disease, Psoriasis, Pemfigus, Pemfigoid, and Dermatitis Herpetiformis.

18. The use according to claim 16, wherein the autoimmune disease is selected from the group consisting of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, gout and osteoarthritis.

19. The use according to claim 12, for the preparation of a medicament for the treatment of IgE-mediated reactions.

20. The use according to claim 19, wherein for the preparation of a medicament for the treatment of asthma, allergic rhinitis, and/or anaphylaxis.

21. The use according to any one of claims 12 to 20, wherein the medicament comprises a composition as defined by any one of claims 5 to 11.

22. The use according to any one of claims 12 to 20, wherein the medicament comprises a chemical complex as defined in any one of claims 1 to 4.

23. The use according to any one of claims 12 to 22, wherein the beta-2 adrenoceptor agonist and the aminosugar are together comprised in a single formulation or are each individually comprised in separate formulations.

24. The use according to any one of claims 12 to 23, wherein the medicament is in a form selected from the group consisting of oral formulation, topical formulation, transdermal formulation, and parenteral formulation.

25. The use according to any one of claims 12 to 24, wherein the mammal is a human.

26. A method for the suppression of hypersensitivity and/or inflammatory reactions in a mammal, comprising the administration to said mammal of a combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, the aminosugar being selected from the group consisting of glucosamine, mannosamine, salts and derivatives thereof, wherein the derivatives thereof is selected from the group consisting of wherein the amino group and/or hydroxyl group of the aminosugar is alkylated, arylated or acylated, and wherein the anomeric, 2-, 3-, 4-, or 6- position is sulphated or phosphorylated.

27. The method according to claim 26, for the treatment or prevention of hypersensitivity skin disease in a mammal.

AMENDED SHEET

28. The method according to claim 27, for the treatment or prevention of atopic eczema, contact dermatitis, seborrhoeic eczema and/or psoriasis.

29. The method according to claim 27, for the treatment or prevention of contact dermatitis or psoriasis.

30. The method according to claim 26 for the treatment or prevention of IgE mediated allergic reaction and/or condition.

31. The method according to claim 30, for the treatment or prevention of asthma, allergic rhinitis, and/or anaphylaxis .

32. The method according to claim 26 for the treatment or prevention of autoimmune disease and/or chronic inflammatory.

33. The method according to claim 32, for the treatment of autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Autoimmune hemolytic anemias, Grave's disease, Myasthenia gravis, Type 1 Diabetes Mellitus, Inflammatory myopathies, Multiple sclerosis, Hashimoto's thyreoiditis, Autoimmune adrenalitis, Crohn's Disease, Ulcerative Colitis, Glomerulonephritis, Progressive Systemic Sclerosis (Scleroderma), Sjögren's Disease, Lupus Erythematosus, Primary vasculitis, Rheumatoid Arthritis, Juvenile Arthritis, Mixed Connective Tissue Disease, Psoriasis, Pemfigus, Pemfigoid or Dermatitis Herpetiformis.

34. The method according to claim 33, for the treatment or prevention of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, gout or osteoarthritis.

35. The method according to any one of claims 26 to 34, wherein the mammal is a human.

36. The method according to claim 26, wherein the combination of the beta-2 adrenoceptor agonist and the aminosugar is a chemical complex as defined in claims 1 to 4.

37. The method according to claim 26, wherein the combination of a beta-2 adrenoceptor agonist and the aminosugar is a composition as defined in any one of claims 5 to 11.

38. The method according to claim 26, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar, or pharmaceutically acceptable salts thereof, are together comprised in a single formulation or are each individually comprised in separate formulations.

39. The method according to claim 26, wherein the combination of a beta-2 adrenoceptor agonist and an aminosugar is administered by means of oral, topical, transdermal, or parenteral administration, or combinations thereof.

40. The method according to claim 38, wherein the separate formulations are administered in a simultaneous or non-simultaneous manner.

41. The method according to claim 26, further comprising administering one or more therapeutically active substances other than the said beta-2 adrenoceptor agonist and said aminosugar.